Nebuliser therapy in the intensive care unit

M J O’Doherty, S H L Thomas

Nebulised drug therapy may be less effective in patients undergoing mechanical ventilation than in those spontaneously breathing for two main reasons – firstly, ventilated patients often have severe lung disease associated with airway plugging and collapsed segments which limit the spread of aerosols to affected areas, and secondly, aerosol deposition from nebulisers and metered dose inhalers is reduced during mechanical ventilation compared with spontaneous breathing.1 This is due to a number of factors including the site of the nebuliser in the ventilator circuit, the ventilator settings, the method of triggering of the nebuliser, and the size of the endotracheal tube. The indications for nebuliser therapy in mechanically ventilated patients are given in table 1.

In ventilated patients compliance is not a problem and it is not necessary for nebulised treatments to be completed rapidly. Indeed, continuous nebulisation may be appropriate for some conditions so nebulisers need not be selected on the basis of rapid output characteristics.

Jet nebulisers tend to leak around their joining parts, especially when used in conjunction with a ventilator. The back pressure necessary to cause leaks should be documented by the manufacturer and users should be encouraged to use systems which do not leak. There is also a need to determine the nebuliser outputs and the particle size produced when attached to the inspiratory limb of the ventilator, the size of the endotracheal tube. The indications for nebuliser therapy in mechanically ventilated patients are given in table 1. In particular, the use of larger bore endotracheal tubes, and a reduced lung inflation rate, may prevent a patient from being able to initiate bronchospasm/asthma.[B]

Methods of aerosol administration

Metered dose inhalers

Bronchodilators and steroids can be delivered during mechanical ventilation using metered dose inhalers, rather than nebulisers.13 These are attached to an adapter in the ventilator circuit and actuated during lung inflation. The method is simple and treatments can be administered rapidly. The amount of drug reaching the lungs has been estimated as 1.5–2% in infants17 and 3.9–5.6% in adults.16 Administration using a metered dose inhaler is increased by using an aerosol holding chamber2 and this method may be more efficient than using an inspiratory phase activated jet nebuliser.27 Arnon et al10 found that the use of a metered dose inhaler and an Aeroschamber (MV15, Trudell Medical, Canada), attached between the Y piece and the endotracheal tube, delivered larger amounts of budesonide to a filter in an in vitro ventilator circuit than either an MAD2 nebuliser or an Ultravent nebuliser. Another study in ventilated patients with airways obstruction has shown that a 270 μg dose of salbutamol given via a metered dose inhaler produces a similar increase in passive expiratory flow rate to that produced by a 2.5 mg dose given by a jet (Upmist) nebuliser.

The factors which appear to increase aerosol delivery to the mechanically ventilated patient from metered dose inhalers are the use of a holding chamber,23,24 locating the metered dose inhaler adapter on the inspiratory limb of the circuit rather than immediately adjacent to the endotracheal tube,23,25 the absence of humidification,22,23 activation during lung inflation,25 the use of larger bore endotracheal tubes,23 and a reduced lung inflation rate.22

Jet nebulisers

Jet nebulisers can be used during pressure limited or volume cycled ventilation. During volume cycled ventilation the ventilator can only be driven during lung inflation. As the gas used to drive the nebuliser forms a proportion of the patient’s tidal volume, its volume and oxygen content must be appropriate for each individual. During pressure limited ventilation the nebuliser can be driven continuously. Jet nebulisers are widely available and cheap, but many are not designed for use during ventilation and leak, particularly at high inflation pressures. During pressure support ventilation the use of a continuously running jet nebuliser may prevent a patient from being able to initiate a ventilator breath as the nebuliser interferes with the achievement of the negative pressure required.24

Aerosol deposition from jet nebulisers has been measured in vivo as 1.2–3.0% in adults.16–18 In vivo data are lacking in infants. For tribavirin administration the continuous use of the small particle aerosol generator (SPAG), consisting of a jet nebuliser and par-
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Nebulisers are used to administer aerosols, especially during mechanical ventilation. The efficiency of aerosol delivery is affected by several factors, including the type of nebuliser used, the configuration of the ventilator circuit, and the patient’s respiratory rate and tidal volume.

**Ultrasonic Nebulisers**

Ultrasonic nebulisers can be used for all types of ventilation and are simpler to use than jet nebulisers, as they do not require gas flow. However, they may not achieve the same level of aerosol deposition as jet nebulisers.

**Clinical Evidence of Benefit from Drug Aerosols**

Evidence that can be used in assessing the potential value of nebulised therapy in ventilated patients, in order of importance, is as follows:

1. **Clinical trials using clinically relevant end points such as survival, length of stay in ITU, length of stay in hospital.**
2. **Clinical trials using physiological measurements such as changes in airway resistance or lung compliance.**
3. **Aerosol deposition and delivery measurements in vivo in man using radio labelled aerosols.**
4. **Aerosol deposition measurements in animals (these are particularly appropriate for paediatric studies although not all lung conditions affecting infants can be mimicked in the lungs of healthy animals and, furthermore, the airway structure of animals differs from that of human infants and therefore the distribution of aerosol may be different).**
5. **Aerosol delivery measurements made in vitro or using combined in vivo/in vitro methods.**

**Recommended Practice**

Any of the following three methods of aerosol administration currently appear to be appropriate for mechanically ventilated patients:

1. **Administration by metered dose inhaler into a spacer connected to the inspiratory limb of the ventilator circuit with actuation at the onset of lung inflation.** Humidification should be interrupted for a few minutes before administration.
2. **Use of an inspiratory phase activated jet nebuliser connected to an aerosol holding chamber placed on the inspiratory limb of the circuit, or at least connected to a Y piece in the inspiratory tubing no more than 30 cm from the Y piece. A high nebuliser gas flow should be used and the drug solution should be diluted to fill the nebuliser to capacity. Humidification should be discontinued for a few minutes before administration.**
3. **Use of an ultrasonic nebuliser connected to the inspiratory limb of the circuit.** The drug solution should be diluted to fill the nebuliser to capacity and humidification should be discontinued for a few minutes before and throughout nebulisation.

**Clinical evidence of benefit from drug aerosols**

Evidence that can be used in assessing the potential value of nebulised therapy in ventilated patients, in order of importance, is as follows:

1. Clinical trials using clinically relevant end points such as survival, length of stay in ITU, length of stay in hospital.
2. Clinical trials using physiological measurements such as changes in airway resistance or lung compliance.
4. Aerosol deposition measurements in animals (these are particularly appropriate for paediatric studies although not all lung conditions affecting infants can be mimicked in the lungs of healthy animals and, furthermore, the airway structure of animals differs from that of human infants and therefore the distribution of aerosol may be different).
5. Aerosol delivery measurements made in vitro or using combined in vivo/in vitro methods using radio labelled or fluorescent aerosols.

These are inevitably overestimates of in vivo lung deposition.

An ideal approach is a combination of these methods. In vitro studies can select those nebulisers worthy of consideration for delivering a particular drug, and then deposition and clinical outcome can be demonstrated in a particular clinical situation. The amount of drug deposited is estimated to prove that sufficient drug is being deposited for clinical benefit.

There are few published studies proving the efficacy of aerosol drug treatments in ventilated patients and it is often necessary to make clinical judgements on the need for aerosol therapy using clinical trial data from spontaneously breathing subjects. This information is used, together with lung deposition or delivery data from patients receiving mechanical ventilation,
to try and predict the usefulness of treatment. Apparatus for which there are research data on deposition or lung deposition during mechanical ventilation are shown in table 2.

**BRONCHOSPASM**

Nebulised β₂ agonists are effective for acute severe asthma in spontaneously breathing patients and their use during mechanical ventilation can also improve measurements of pulmonary function (respiratory system resistance, compliance) in adults and infants with acute asthma, although not all studies have shown this. Pulmonary function can also be improved in adults with chronic obstructive pulmonary disease. No clinical trials have been performed to compare different bronchodilator or aerosol methods of aerosol administration. In some patients delivery of aerosol to peripheral bronchioles may be particularly poor because of intense bronchospasm and it may often be appropriate to use intravenous as well as inhaled bronchodilators in patients with severe disease. Ipratropium bromide also improves pulmonary function in mechanically ventilated patients with COPD.

**RESPIRATORY Syncytial VIRUS (RSV) infection**

Clinical trials have been performed in infants with respiratory failure associated with RSV infection, evaluating the efficacy of continuous nebulised tribuvirin (20 mg/ml) using the SPAG. This consists of a jet nebuliser coupled to a particle drying tube. In one study infants treated with nebulised tribuvirin had reduced durations of mechanical ventilation, oxygen treatment, and hospital stay compared with infants treated with nebulised water. In a second study infants treated with nebulised tribuvirin had small reductions in the duration of mechanical ventilation, supplemental oxygen use, and hospital stay compared with those receiving nebulised saline. However, the differences were not statistically significant, although a clinically relevant drug effect may have been missed because of reduced study power. Other possible explanations for the apparent differences in the findings of these studies are that the nebulised water used as a placebo in the first study may have had a deleterious effect on lung function. Alternatively, treatment with tribuvirin may have been commenced too late for maximum benefit in the second study. Neither study included patients with apnoea and the effects of nebulised tribuvirin in this group have not been assessed. Further studies using larger patient numbers, different doses, and different methods of administration will be needed to clarify the role of nebulised tribuvirin in severe RSV infection. This topic is discussed further in the chapter on nebuliser treatment in childhood on pages S78-88.

The SPAG, as well as being cumbersome to use, is an inefficient method for delivering aerosol (0.1±0.5 μm) compared with other methods and its particle size output is comparatively large (mass median aerodynamic diameter (MMAD) 6.8 μm). Other devices may be better for delivering tribuvirin but this has yet to be proved.

Tribuvirin may deposit in ventilator circuits and block the expiratory valve, leading to expiratory pressures and barotrauma. This should be avoided by appropriate use of filters to protect the ventilator from the effects of the aerosol.

**BRONCHOPULMONARY DYSPLASIA**

Nebulised beclomethasone 50 μg eight hourly for 28 days reduced arterial oxygen and increased dynamic compliance in infants with bronchopulmonary dysplasia. Beclomethasone was administered using a Whisper (Marquest Medical Products, Englewood, Colorado, USA) jet nebuliser on the inspiratory limb of the circuit and running at 4±8 l/min of humidified gas. Pulmonary deposition was not measured. Beclomethasone dipropionate nebuliser solution is no longer produced but it is to be expected that beclomethasone delivered by metered dose inhaler or an alternative nebulised steroid such as budesonide should provide similar benefit. Further studies confirming the value of this form of treatment are needed.

**ADULT Respiratory Distress SYNDROME (ARDS)**

Preliminary evidence suggests that nebulised colfosceril palmitate (40-80 mg) given continuously over five days may improve the alveolar-arterial oxygen tension gradient (A–aDO₂) and fractional inspired oxygen (FiO₂) and reduce mortality in adults with sepsis-induced ARDS. Weg et al also used nebulised colfosceril palmitate in a group of patients with ARDS for 12 or 24 hours per day and found a trend towards improvement in mortality compared with no treatment.

Nebulised orciprenaline (metaproterenol) has been shown to reduce arterial oxygen in patients with ARDS.

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Table 2 Nebulisers for which there are research data on deposition achieved with nebulised saline, water, or drug solutions

<table>
<thead>
<tr>
<th>Nebuliser</th>
<th>Manufacturer</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Aerotech II</td>
<td>CIS-US, Bedford, MA, USA</td>
<td>22</td>
</tr>
<tr>
<td>Acorn jet nebuliser</td>
<td>Whisper, Appleton, WI, USA</td>
<td>25, 27, 28</td>
</tr>
<tr>
<td>Ascend</td>
<td>System 22, Medical-Aid, Pagham, West Sussex, UK</td>
<td>25</td>
</tr>
<tr>
<td>DF100</td>
<td>DF Medical, Maylan, France</td>
<td>56</td>
</tr>
<tr>
<td>DF200</td>
<td>DF Medical, Maylan, France</td>
<td>55</td>
</tr>
<tr>
<td>Aerosol II</td>
<td>CritiCare, Minneapolis, MN, USA</td>
<td>22</td>
</tr>
<tr>
<td>Tracneb</td>
<td>Patterson-Price, London, UK</td>
<td>16, 22</td>
</tr>
<tr>
<td>Respiraid</td>
<td>Marquest, Englewood, CO, USA</td>
<td>22</td>
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<tr>
<td>Proven</td>
<td>Hospitak, Lindenhurst, NY, USA</td>
<td>23</td>
</tr>
<tr>
<td>Whisper</td>
<td>Marquest, Englewood, CO, USA</td>
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<tr>
<td>UltraNeb</td>
<td>DeVilbiss, USA</td>
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<tr>
<td>Acorn jet nebuliser</td>
<td>System 22, Medic-Aid, Pagham, West Sussex, UK</td>
<td>16, 22, 25, 27, 28</td>
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<tr>
<td>Low flow nebuliser</td>
<td>Baxter Healthcare, McGaw Park, IL, USA</td>
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<tr>
<td>MAD II</td>
<td>Astra Meditec, Lund, Sweden</td>
<td>18, 35</td>
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</tbody>
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